# EXHIBIT 1

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Paper: Request for Reconsideration, Transmittal Form, Fee Transmittal (in duplicate), return card all sent via U.S. First Class Mail

Applicant(s): Stephen Donovan

Title: Transdermal Botulinum Toxin Administration

Serial No: 09/675,172 Filing Date: September 29, 2003

Docket No. ALLE0016-102 (17510 DIV2) [165596]

Date Sent: Oct 31/05

By: Quan L. Nguyen/cda

NOV 8 2005

OIPE IAP59 NOV 02 2005 PATENT & TRADEMARK OFFICE

PTO/SB/21 (09-04)
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U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE


# TRANSMITTAL FORM

*(to be used for all correspondence after initial filing)*

Total Number of Pages in This Submission

| | |
|---|---|
| Application Number | 09/675,172 |
| Filing Date | September 29, 2003 |
| First Named Inventor | Stephen Donovan |
| Art Unit | 1645 |
| Examiner Name | Vanessa L. Ford |
| Attorney Docket Number | ALLE0016-102 (17510 DIV2) [165596] |

**ENCLOSURES** *(check all that apply)*

- ☒ Fee Transmittal Form
  - ☐ Fee Attached
- ☒ Amendment / Reply
  - ☐ After Final
  - ☐ Affidavits/declaration(s)
- ☐ Extension of Time Request
- ☐ Express Abandonment Request
- ☐ Information Disclosure Statement
- ☐ Certified Copy of Priority Document(s)
- ☐ Reply to Missing Parts/ Incomplete Application
  - ☐ Reply to Missing Parts under 37 CFR1.52 or 1.53
- ☐ Drawing(s)
- ☐ Licensing-related Papers
- ☐ Petition
- ☐ Petition to Convert to a Provisional Application
- ☐ Power of Attorney, Revocation Change of Correspondence Address
- ☐ Terminal Disclaimer
- ☐ Request for Refund
- ☐ CD, Number of CD(s) _____
  - ☐ Landscape Table on CD
- ☐ After Allowance Communication to TC
- ☐ Appeal Communication to Board of Appeals and Interferences
- ☐ Appeal Communication to TC (Appeal Notice, Brief, Reply Brief)
- ☐ Proprietary Information
- ☐ Status Letter
- ☐ Other Enclosure(s) *(please identify below)*:

Remarks

**SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT**

| | | | |
|---|---|---|---|
| Firm | Cozen O'Connor | | |
| Signature | | | |
| Printed Name | Quan L. Nguyen | | |
| Date | 10/31/06 | Reg. No. | 46,957 |

**CERTIFICATE OF TRANSMISSION/MAILING**

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| Signature | | | |
| Typed or printed name | Quan L. Nguyen | Date | 10/31/06 |

*Effective on 12/08/2004.*
*Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).*

# FEE TRANSMITTAL for FY 2005

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 0

| Complete if Known | |
|---|---|
| Application Number | 09/675,172 |
| Filing Date | September 29, 2003 |
| First Named Inventor | Stephen Donovan |
| Examiner Name | Vanessa L. Ford |
| Art Unit | 1645 |
| Attorney Docket No. | ALLE0016-102 (17510 DIV2) [165596] |

**METHOD OF PAYMENT** (check all that apply)

☐ Check ☐ Credit Card ☐ Money Order ☐ None ☐ Other (please identify) :

☒ Deposit Account Deposit Account Number: 50-1275 Deposit Account Name: Cozen O'Connor

For the above-identified deposit account, the Director is hereby authorized to: (check all that apply)

☒ Charge fee(s) indicated below ☐ Charge fee(s) indicated below, except for the filing fee

☒ Charge any additional fee(s) or underpayments of fee(s) Under 37 CFR 1.16 and 1.17 ☒ Credit any overpayments

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**FEE CALCULATION**

**1. BASIC FILING, SEARCH, AND EXAMINATION FEES**

| | FILING FEES | Small Entity | SEARCH FEES | Small Entity | EXAMINATION FEES | Small Entity | |
|---|---|---|---|---|---|---|---|
| Application Type | Fee ($) | Fee($) | Fee($) | Fee($) | Fee($) | Fee($) | Fees Paid ($) |
| Utility | 300 | 150 | 500 | 250 | 200 | 100 | ____ |
| Design | 200 | 100 | 100 | 50 | 130 | 65 | ____ |
| Plant | 200 | 100 | 300 | 150 | 160 | 80 | ____ |
| Reissue | 300 | 150 | 500 | 250 | 600 | 300 | ____ |
| Provisional | 200 | 100 | 0 | 0 | 0 | 0 | ____ |

**2. EXCESS CLAIM FEES**

| Fee Description | Fee ($) | Small Entity Fee ($) |
|---|---|---|
| Each claim over 20 (including Reissues) | 50 | 25 |
| Each independent claim over 3 (including Reissues) | 200 | 100 |
| Multiple dependent claims | 360 | 180 |

| Total Claims | Extra Claims | Fee($) | Fee Paid ($) |
|---|---|---|---|
| 9 - HP = 35 | 0 | x 0 | = 0 |

HP = highest number of total claims paid for, if greater than 20.

| Indep. Claims | Extra Claims | Fee($) | Fee Paid ($) |
|---|---|---|---|
| 1 - 3 or HP= | 0 | x 0 | = |

HP = highest number of independent claims paid for, if greater than 3.

| Multiple Dependent Claims | |
|---|---|
| Fee ($) | Fee Paid ($) |
| ____ | ____ |

**3. APPLICATION SIZE FEE**

If the specification and drawings exceed 100 sheets of paper (excluding electronically filed sequence or computer listings under 37 CFR 1.52(c)), the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

| Total Sheets | Extra Sheets | Number of each additional 50 or fraction thereof | Fee ($) | Fee Paid ($) |
|---|---|---|---|---|
| ____ - 100 = | ____ | / 50 = ____ (round up to a whole number) x | | = ____ |

**4. OTHER FEE(S)**

| | Fees Paid ($) |
|---|---|
| Non-English Specification, $130 fee (no small entity discount) | ____ |
| Other (e.g., late filing surcharge) : ____ | ____ |

**SUBMITTED BY**

| | | | |
|---|---|---|---|
| Signature | | Registration No. (Attorney/Agent) 48,857 | Telephone 215-665-2168 |
| Name (Print/Type) | Quan L. Nguyen | | Date 10/21/05 |

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| Examiner Name | Vanessa L. Ford |
| Art Unit | 1645 |
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For the above-identified deposit account, the Director is hereby authorized to: (check all that apply)

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☒ Charge any additional fee(s) or underpayments of fee(s) Under 37 CFR 1.16 and 1.17 ☒ Credit any overpayments

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## FEE CALCULATION

### 1. BASIC FILING, SEARCH, AND EXAMINATION FEES

| | FILING FEES | | SEARCH FEES | | EXAMINATION FEES | | |
|---|---|---|---|---|---|---|---|
| | | Small Entity | | Small Entity | | Small Entity | |
| Application Type | Fee ($) | Fee($) | Fee($) | Fee($) | Fee($) | Fee($) | Fees Paid ($) |
| Utility | 300 | 150 | 500 | 250 | 200 | 100 | ____ |
| Design | 200 | 100 | 100 | 50 | 130 | 65 | ____ |
| Plant | 200 | 100 | 300 | 150 | 160 | 80 | ____ |
| Reissue | 300 | 150 | 500 | 250 | 600 | 300 | ____ |
| Provisional | 200 | 100 | 0 | 0 | 0 | 0 | ____ |

### 2. EXCESS CLAIM FEES

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|---|---|---|
| Each claim over 20 (including Reissues) | 50 | 25 |
| Each independent claim over 3 (including Reissues) | 200 | 100 |
| Multiple dependent claims | 360 | 180 |

| Total Claims | | Extra Claims | | Fee($) | | Fee Paid ($) |
|---|---|---|---|---|---|---|
| 9 | - HP = 35 | 0 | x | 0 | = | 0 |

HP = highest number of total claims paid for, if greater than 20.

| Indep. Claims | | Extra Claims | | Fee($) | | Fee Paid ($) |
|---|---|---|---|---|---|---|
| 1 | - 3 or HP= | 0 | x | 0 | = | |

HP = highest number of independent claims paid for, if greater than 3.

| Multiple Dependent Claims | | |
|---|---|---|
| | Fee ($) | Fee Paid ($) |
| | ____ | ____ |

### 3. APPLICATION SIZE FEE

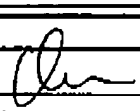
If the specification and drawings exceed 100 sheets of paper (excluding electronically filed sequence or computer listings under 37 CFR 1.52(a)), the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

| Total Sheets | | Extra Sheets | | Number of each additional 50 or fraction thereof | | Fee ($) | | Fee Paid ($) |
|---|---|---|---|---|---|---|---|---|
| ____ | - 100 = | ____ | / 50 = | ____ | (round up to a whole number) x | | = | ____ |

### 4. OTHER FEE(S)

| | Fees Paid ($) |
|---|---|
| Non-English Specification, $130 fee (no small entity discount) | ____ |
| Other (e.g., late filing surcharge) : ____ | ____ |

## SUBMITTED BY

| | | | |
|---|---|---|---|
| Signature |  | Registration No. (Attorney/Agent) 46,957 | Telephone 215-665-2150 |
| Name (Print/Type) | Quan L. Nguyen | | Date 10/21/05 |

This collection of information is required by 37 CFR 1.136. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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**DOCKET NO.: ALLE0016-102**
**(17510 DIV2)**

**PATENT**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | | | |
|---|---|---|---|
| In re application of: | | Examiner: | |
| **Stephen Donovan** | | **Vanessa L. Ford** | |
| Serial No.: | **09/675,172** | Group Art Unit: | **1645** |
| Filed: | **September 29, 2003** | Confirmation No. | **5916** |

For: **TRANSDERMAL BOTULINUM TOXIN ADMINISTRATION**

**Commissioner for Patents**
**P.O. Box 1450**
**Alexandria, VA 22313-1450**

**Dear Sir:**

## REQUEST FOR RECONSIDERATION

In response to the Office Action mailed July 29, 2005, in connection with the above-identified patent application, Applicant respectfully requests reconsideration of the rejections of record in view of the remarks provided below.

**DOCKET NO.: ALLE0016-102** **PATENT**
**(17510 DIV2)**

**Listing of Claims**

This listing of claims will replace all prior versions, and listings, of claims in the application:

1-21. (canceled).

22. (original) A method of reducing neurotransmitter release in a subdermal structure of a patient, the method comprising the steps of:

(a) non-chemically disrupting the stratum corneum of the patient's skin to reduce impermeability of the stratum corneum; and

(b) applying botulinum toxin to the skin of the patient in an area that has had the stratum corneum disrupted in step (a).

23. (original) The method of claim 22, wherein the stratum corneum is disrupted by abrasively removing the stratum corneum.

24. (original) The method of claim 22, wherein the stratum corneum is disrupted by applying an adhesive material to the patient's skin, and removing the adhesive material applied thereto.

25. (original) The method of claim 22, wherein the stratum corneum is disrupted by applying ultrasound at a frequency between 20 kHz and less than 10 MHz at an intensity that does not permanently damage the patient's skin.

26. (original) The method of claim 22, wherein the stratum corneum is disrupted by passing electrical current from a first point on the patient's skin to a second point on the patient's skin.

27. (original) The method of claim 26, wherein the electrical current is passed to create a plurality of pores in the stratum corneum to enhance passage of botulinum toxin to the subdermal structures.

28. (original) The method of claim 22, wherein the botulinum toxin is selected from a group of botulinum toxins consisting of types A, B, C, D, E, F and G.

29. (original) The method of claim 22, wherein the botulinum toxin is applied in a pharmaceutical composition comprising an enhancing agent for enhancing the delivery of the botulinum toxin through the skin.

30. (original) The method of claim 22, wherein the botulinum toxin is incorporated into a transfersome.

31-35 (canceled).

**DOCKET NO.: ALLE0016-102** **PATENT**
**(17510 DIV2)**

## REMARKS

Upon entry of the above amendment, claims 22-30 will be pending in this application.

**Yuzhakov et al. Is Not Prior Art**

Claims 22 and 26-29 stand rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Pat. No. 6,565,532 to Yuzhakov et al. (hereinafter "the Yuzhakov reference"). Applicant respectfully asserts the claimed invention is novel because the Yuzhakov reference cannot be an anticipating prior art under 35 U.S.C. § 102(e). Specifically, 35 U.S.C. § 102(e) states that an applicant is entitled to a patent, unless:

> the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371 (c) of this title [35 USC §371(c)(1), (2), (4)] before the invention thereof by the applicant for patent...

Thus, a reference can only be prior art under 102(e) if it is granted **before** to the priority date of the claimed invention. The Yuzhakov reference cannot be an anticipating prior art reference under 102(e) because its **grant date of May 20, 2003 is after** the invention date of the present application, which is as least as early as **July 11, 2002** (see Preliminary Amendment filed on September 29, 2003, which amended the specification to state that the present application is a divisional of U.S. Application Serial No. 10/194,805 which was filed July 11, 2002). Accordingly, the claimed invention is novel.

**The Claims Are Nonobvious**

Claims 22-30 stand rejected under 35 U.S.C. § 102(e) as allegedly being obvious over the Yuzhakov reference in view of Mitragotri et al. (Science, Vol. 269, August 11,

1995, hereinafter "the Mitragotri reference"), U.S. Patent No. 5,587,396 (hereinafter "the Smith reference"), and/or U.S. Patent No. 6,165,500 (hereinafter "the Cevc reference").

The Office Action cites the Yuzhakov reference as the primary reference. However, as stated above, the Yuzhakov reference cannot be cited as prior art. As such, the rejection for obviousness would be based entirely on the cited secondary references. However, none of the secondary references by itself, or in combination with other references, teach or suggest the claimed invention. For example, the claimed invention recites the steps of **non-chemically disrupting** the stratum corneum and applying a **botulinum toxin** to the disrupted stratum corneum for the botulinum toxin to penetrate to a **subdermal layer** of the patient skin. Botulinum toxin is about 150 kDa by itself, and is about 900 kDa when it is associated with other non-toxin proteins to form a complex.

The **Mitragotri** reference, however, does not teach or suggest a method for delivery of proteins having at least a molecular weight of 150 kDa, much less a botulinum toxin. Instead, the Mitragotri reference only teaches transdermal delivery of proteins between the molecular weights of 6 kDa and 48 kDa. The Mitragotri reference at page 850.

The **Smith** reference relates to a method for treating a cellulite condition using a "cell renewal stimulant". Accordingly, the Smith reference teaches that a skin area can be stripped prior to applying a cell renewal stimulant (e.g., a retinoid, see claim 1). However, the Smith reference does not teach or suggest that an enzyme such as botulinum toxin may be applied to the stripped skin area, where the enzyme would penetrate to the subdermal layer of the skin. Further, from reading the specification of the Smith reference, one of ordinary skill would not be motivated to apply a botulinum toxin to the stripped area of skin, because a retinoid and a botulinum toxin are very different from each other and would be expected to have different skin penetration properties. For example, a retinoid (e.g., vitamin A) is a small molecule with a molecular weight of about 0.30 kDa., whereas the molecular weight of a botulinum toxin is about 150 kDa (900 kDa for the botulinum toxin complex). Since the penetration of molecules

**DOCKET NO.: ALLE0016-102**
**(17510 DIV2)**

**PATENT**

through stripped skin partly depend on their sizes, one would have no basis to expect that botulinum toxin would penetrate through the stripped skin similarly to that of a retinoid, because botulinum toxin is much larger than the retinoid. Thus, the claimed invention is not obvious over the Smith reference alone, or in combination with the other secondary references.

The Ceve reference alone, or in combination with the other secondary references, fails to teach or suggest the step of non-chemically disrupting a skin area in conjunction with the application of a botulinum toxin, much less that such step will allow for the botulinum toxin to penetrate to the subdermal layer of the skin.

In view of the foregoing, Applicants submit that the pending claims are in condition for allowance, and an early Office Action to that effect is earnestly solicited.

Respectfully submitted,

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Registration No. 46,957

Date: October 31, 2005

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